

Amended Claims

1-48. (canceled)

49. (Withdrawn) A method of treating or preventing a disorder selected from the group consisting of disorders in which treatment with an ACE-inhibitor is indicated, cardiovascular disorders, renal disorders, and diabetes associated disorders, in a mammal in need of said treating or preventing, comprising administering to said mammal an effective amount of a multifunctional ACE-inhibitor comprising in one molecule

- i) an ACE-inhibitor component;
- ii) at least one reactive oxygen species (ROS) scavenger component, not identical with said ACE-inhibitor component; and optionally,
- iii) at least one nitric oxide (NO) donor component, not identical with said ROS scavenger component.

50. (Withdrawn) A method according to claim 49, wherein said multifunctional ACE-inhibitor comprises

- i) an ACE-inhibitor component;
- ii) at least one ROS-scavenger component not identical with said ACE-inhibitor component; and
- iii) at least one nitric oxide (NO) donor component, not identical with said ROS scavenger component.

51. (Withdrawn) A method according to claim 49, wherein said ACE-inhibitor component is selected from the group consisting of compounds used in medicine as ACE-inhibitors, derivatives thereof, and compounds exhibiting affinity for ACE.

52. (Withdrawn) A method according to claim 49, wherein said ROS-scavenger component comprises an antioxidant reacting with an ROS selected from the group consisting of superoxide, hydroxyl radicals, peroxyinitrite, and hypochlorite.

53. (Withdrawn) A method according to claim 49, wherein said ROS-scavenger component comprises an alkenyl group, aryl group, substituted aryl group, sulfhydryl, dithiol in oxidized or reduced form, or a group that is converted in vivo into a sulfhydryl in its oxidized or reduced form.

54. (Withdrawn) A method according to claim 49, wherein said ROS-scavenger component comprises a substituted N-oxide free radical, or a substituted or unsubstituted lipoic acid moiety.

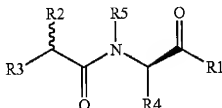
55. (Withdrawn) A method according to claim 49, wherein said ROS-scavenger component comprises an N-oxide free radical, wherein the nitrogen of said N-oxide free radical is within a 3-, 4-, 5-, 6- or 7-membered ring, and wherein the ring may be substituted or unsubstituted with straight or branched alkyl groups, alkoxy groups or groups capable of donating NO.

56. (Withdrawn) A method according to claim 49, wherein said NO-donor comprises a group capable of providing nitric oxide in a form selected from uncharged and charged.

57. (Withdrawn) A method according to claim 49, wherein said NO-donor component comprises a group selected from --ONO<sub>2</sub>, --ONO, --SNO, and --NONOate.

58. (Withdrawn) A method according to claim 49, wherein said ACE-inhibitor component is derived from an ACE-inhibitor selected from the group consisting of Alacepril, Benazepril, Captopril, Ceronapril, Cilazapril, Delapril, Enalapril, Enalaprilat, Fosinopril, Imidapril, Lisinopril, Moveltopril, Perindopril, Quinapril, Ramipril, Spirapril, Temocapril, and Trandolapril.

59. (Withdrawn) A method according to claim 49, wherein said multifunctional ACE-inhibitor has Formula I:

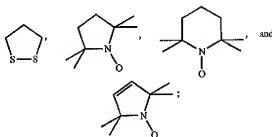


wherein

R<sup>1</sup> may be selected from H, OH, NH<sub>2</sub>, and alkoxy;

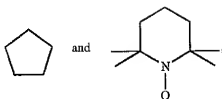
R<sup>2</sup> may be selected from --H and lower alkyl;

R<sup>3</sup> may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:

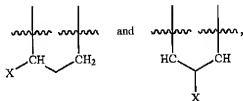


R<sup>4</sup> may be lower alkyl or H;

R<sup>5</sup> may be selected from --H, lower alkyl, -alkylene-Y or Y, wherein Y is a radical selected from the group consisting of:

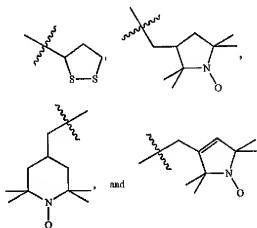


or  $R^4$  and  $R^5$  together may form a group selected from the formulae:

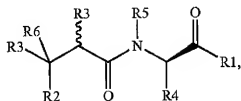


wherein X is selected from H, OH, SH, NH<sub>2</sub>, ONO<sub>2</sub>, SNO and NONOate.

60. (Withdrawn) A method according to claim 59, wherein said R<sub>sup.3</sub> is selected from



61. (Withdrawn) A method according to claim 49, wherein said multifunctional ACE-inhibitor has Formula II:

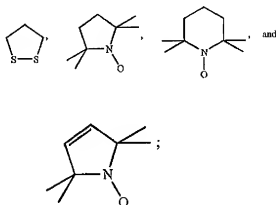


wherein

$R^1$  may be selected from H, OH,  $NH_2$ , and alkoxy;

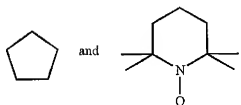
$R^2$  may be independently selected from SH and SNO;

$R^3$  may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:

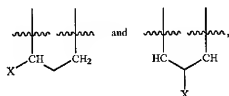


$R^4$  may be lower alkyl or H;

$R^5$  may be selected from H, lower alkyl, -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:



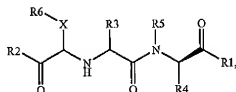
or  $R^4$  and  $R^5$  together may form a group selected from the formulae:



wherein X is selected from H, OH, SH,  $NH_2$ ,  $ONO_2$ , SNO and NONOate; and

$R^6$  may be lower alkyl.

62. (Withdrawn) A method according to claim 49, wherein said multifunctional ACE-inhibitor has Formula III:



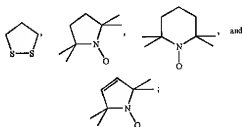
wherein

$R^1$  may be selected from OH,  $NH_2$ , alkoxy, and alkyl;

$R^2$  may be selected from OH,  $NH_2$ , alkoxy, and alkyl;

$R^3$  is lower alkyl; and

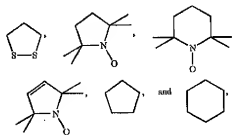
$R^6$  may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:



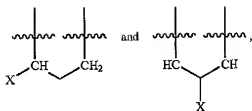
X is  $(CH_2)_n$ , where n an integer from 0 to 5;

$R^4$  is lower alkyl or H;

$R^5$  may be selected from H, lower alkyl, -alkylene-Y, and Y, wherein Y is a radical selected from the group consisting of:

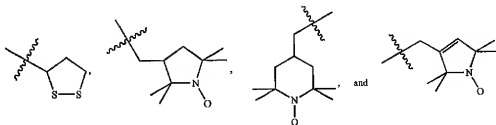


or  $R^4$  and  $R^5$  together form a group independently selected from the formulae:

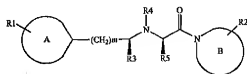


wherein X is selected from H, OH, SH, NH<sub>2</sub>, ONO<sub>2</sub>, SNO, and NONOate.

63. (Withdrawn) A method according to claim 62, wherein said R<sup>6</sup> is selected from



64. (Withdrawn) A method according to claim 49, wherein said multifunctional ACE-inhibitor has Formula IV:



wherein m is an integer from 0 to 5;

A and B are, independently, optionally substituted saturated or unsaturated rings of from 4 to 18 atoms, wherein one or both comprise said ROS scavenger component; and wherein

R<sup>1</sup> and R<sup>5</sup> are, independently, selected from H, optionally substituted lower alkyl, and (CH<sub>2</sub>)<sub>n</sub>X, where n is 0-2 and X is selected from OH, NH<sub>2</sub>, SH, ONO, ONO<sub>2</sub>, SNO and NONOate;

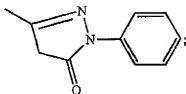
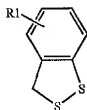
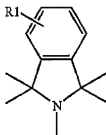
R<sup>2</sup> and R<sup>3</sup> are, independently, selected from COR<sup>6</sup> and (CH<sub>2</sub>)<sub>n</sub>X, wherein R<sup>6</sup> is selected from the group consisting of OH, optionally substituted alkyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, n is 0-2, and X is selected from OH, NH<sub>2</sub>, SH, ONO, ONO<sub>2</sub>, SNO, and NONOate;

R<sup>4</sup> is H or lower alkyl;

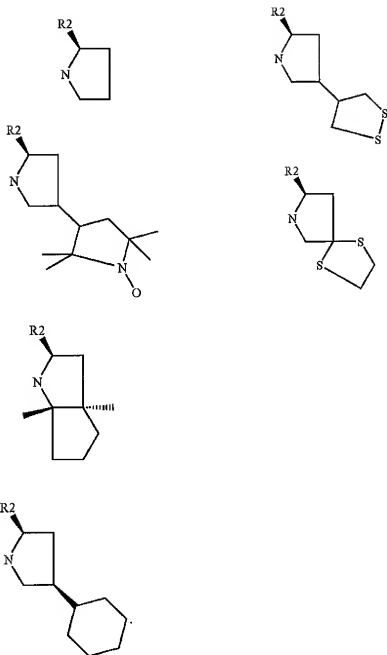
A is an optionally substituted saturated or unsaturated ring system of from 4 to 18 atoms; and

B is an optionally substituted, saturated or unsaturated ring system of from 4 to 18 atoms.

65. (Withdrawn) A method according to claim 64, wherein A is selected from the group consisting of



and B is selected from the group consisting of



66. (Withdrawn) A method according to claim 49, wherein said disorder is selected from the group consisting of ischaemic heart disease, angina pectoris, myocardial infarction, congestive heart failure, cardiomyopathy, atherosclerosis, ischaemia-reperfusion tissue injury, peripheral vascular disease, critical limb ischaemia, palpitations, arrhythmia, tachycardia, sinus, thyrotoxicosis, pheochromocytoma, tension, anxiety, alcohol withdrawal, anxiety, migraine, arterial aneurysm, microvascular diseases, hypertension selected from pulmonary-, systemic-, ocular-, obesity-, and pregnancy-induced, impotence, diabetes mellitus, hypercholesteremia, Reaven's syndrome, diabetic nephropathy, insulin-resistance and glucose intolerance in diabetes, endothelial



dysfunction or oxidative stress-induced diseases, drug or disease induced nephropathy, and esophageal varices.

67. (Withdrawn) A method according to claim 66, further preventing the occurrence of adverse effects of drugs, the development of tolerance to drugs, or the development of hypersensitivity to drugs.

68. (Withdrawn) A method according to claim 49, wherein said administering is selected from the group consisting of topical, oral, and parenteral.

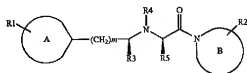
69. (Withdrawn) A method according to claim 49, wherein said administering is selected from the group consisting of suppository, by way of injection, and by way of infusion.

70. (Withdrawn) A method according to claim 49, wherein said multifunctional ACE-inhibitor is administered by a route selected from intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, implant, inhalation spray, nasal, vaginal, rectal, sublingual, and urethral.

71. (Withdrawn) A method according to claim 49, wherein said mammal is human.

72. (Previously Presented) A multifunctional ACE-inhibitor comprising  
 i) an ACE-inhibitor component,  
 ii) at least one reactive oxygen species (ROS) scavenger component, not identical with said ACE-inhibitor component, and  
 iii) at least one nitric oxide (NO) donor component, not identical with said ROS scavenger component

wherein said multifunctional ACE-inhibitor has Formula IV:



wherein m is an integer from 0 to 5;

A and B are, independently, optionally substituted saturated or unsaturated rings of from 4 to 18 atoms, wherein one or both comprise said ROS scavenger component; and wherein

R<sup>1</sup> and R<sup>5</sup> are independently selected from H, substituted lower alkyl, and (CH<sub>2</sub>)<sub>n</sub>X, where n is 0-2 and X is selected from OH, NH<sub>2</sub>, SH, ONO, ONO<sub>2</sub>, SNO and NONOate;

R<sup>2</sup> and R<sup>3</sup> are independently selected from COR<sup>6</sup> and (CH<sub>2</sub>)<sub>n</sub>X, wherein R<sup>6</sup> is selected from the group consisting of OH, optionally substituted alkyl, optionally substituted acyl, optionally substituted aryl, optionally substituted

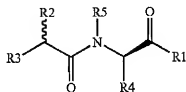
heterocyclyl, and optionally substituted cycloalkyl, n is 0-2, and X is selected from OH, NH<sub>2</sub>, SH, ONO, ONO<sub>2</sub>, SNO, and NONOate;

R<sup>4</sup> is H or lower alkyl;

A is an optionally substituted saturated or unsaturated ring system of from 4 to 18 atoms; and

B is an optionally substituted, saturated or unsaturated ring system of from 4 to 18 atoms.

73. (Withdrawn) A multifunctional ACE-inhibitor according to claim 72 having Formula I:

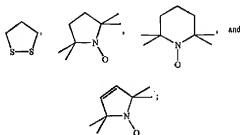


wherein

R<sup>1</sup> may be selected from H, OH, NH<sub>2</sub>, and alkoxy;

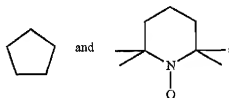
R<sup>2</sup> may be selected from H and lower alkyl;

R<sup>3</sup> may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:

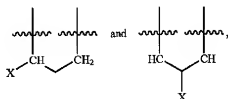


R<sup>4</sup> may be lower alkyl or H;

R<sup>5</sup> may be selected from H, lower alkyl, -alkylene-Y or Y, wherein Y is a radical selected from the group consisting of:

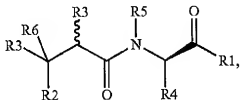


or  $R^4$  and  $R^5$  together may form a group selected from the formulae:



wherein X is selected from H, OH, SH,  $NH_2$ ,  $ONO_2$ , SNO and NONOate.

74. (Withdrawn) A multifunctional ACE-inhibitor according to claim 72 having Formula II:

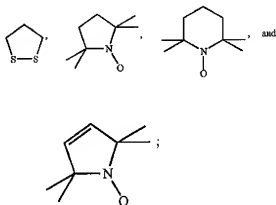


wherein

$R^1$  may be selected from H, OH,  $NH_2$ , and alkoxy;

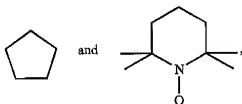
$R^2$  may be independently selected from SH and SNO;

$R^3$  may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:

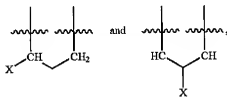


$R^4$  may be lower alkyl or H;

$R^5$  may be selected from H, lower alkyl, -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:

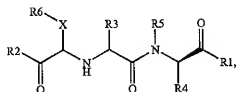


or  $R^4$  and  $R^5$  together may form a group selected from the formulae:



wherein X is selected from H, OH, SH, NH<sub>2</sub>, ONO<sub>2</sub>, SNO and NONOate; and  $R^6$  may be lower alkyl.

75. (Withdrawn) A multifunctional ACE-inhibitor according to claim 72 having Formula III:



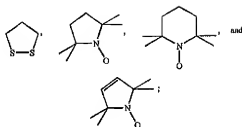
wherein

$R^1$  may be selected from OH, NH<sub>2</sub>, alkoxy, and alkyl;

$R^2$  may be selected from OH, NH<sub>2</sub>, alkoxy, and alkyl;

$R^3$  is lower alkyl; and

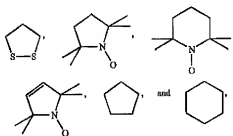
$R^6$  may be selected from -alkylene-Y and Y, wherein Y is a radical selected from the group consisting of:



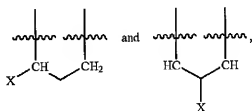
X is  $(CH_2)_n$ , where n an integer from 0 to 5;

$R^4$  is lower alkyl or H;

$R^5$  may be selected from H, lower alkyl, -alkylene-Y, and Y, wherein Y is a radical selected from the group consisting of:

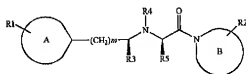


or  $R^4$  and  $R^5$  together form a group independently selected from the formulae:



wherein X is selected from H, OH, SH,  $NH_2$ ,  $ONO_2$ , SNO, and NONOate.

76. (Withdrawn) A multifunctional ACE-inhibitor according to claim 72 having Formula IV:



wherein m is an integer from 0 to 5;

A and B are, independently, optionally substituted saturated or unsaturated rings of from 4 to 18 atoms, wherein one or both comprise said ROS scavenger component; and wherein

$R^1$  and  $R^5$  are, independently, selected from H, optionally substituted lower alkyl, and  $(CH_2)_nX$ , where n is 0-2 and X is selected from OH,  $NH_2$ , SH, ONO,  $ONO_2$ , SNO and NONOate;

$R^2$  and  $R^3$  are, independently, selected from  $COR^6$  and  $(CH_2)_nX$ , wherein  $R^6$  is selected from the group consisting of OH, optionally substituted alkyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, and optionally substituted cycloalkyl, n is 0-2, and X is selected from OH,  $NH_2$ , SH, ONO,  $ONO_2$ , SNO, and NONOate;

$R^4$  is H or lower alkyl;

A is an optionally substituted saturated or unsaturated ring system of from 4 to 18 atoms; and

B is an optionally substituted, saturated or unsaturated ring system of from 4 to 18 atoms.

77. (Previously Presented) A pharmaceutical composition comprising an ACE-inhibitor according to claim 72, or a derivative thereof selected from the group consisting of an optical isomer, solvate, and salt.

78. (Previously Presented) A pharmaceutical composition according to claim 77 further comprising a component selected from the group consisting of a carrier, binding agent, stabilizer, adjuvant, diluent, excipient, surfactant, odorant, and a second pharmaceutically active agent.

79. (Withdrawn) A kit for administering a multifunctional ACE-inhibitor comprising

- i) a dosage amount of at least one compound having a component exhibiting ACE-inhibitor activity and another component exhibiting ROS-scavenging activity;
- ii) instructions for use; and
- iii) optionally, means for delivery of said compound.